REMARKS

Telephone Interview

Applicants would like to express their appreciation to Examiner Huynh and Examiner Chan for the courtesy extended to Angela Sebor during the telephone interview of October 6, 2004. During the interview, the rejections under 35 U.S.C. § 112, first paragraph and § 103 were discussed. Specifically, with regard to the § 112 rejections, the Examiners suggested that the CGRP agents to be used in the claimed method be more specifically defined in terms of function, so that it is clear that the agents are agonists and could not encompass antagonists of CGRP. Second, with regard to the § 103 rejection, the reference of Cadieux et al. was discussed, and particularly, Figure 2 and Table 1 of this publication. Applicants agreed to present further arguments and amendments to clearly distinguish the present claims from the Cadieux et al. publication.

Claim Amendments:

Support for defining CGRP activity as "binds to and activates a CGRP receptor" in amended Claims 1, 39, 40 and new Claim 46 is found in the specification, for example, on page 12, lines 9-12; page 20, lines 7-8; page 26, line 24-27.

Support for referencing that the homologue or fragment is an agonist of CGRP in amended Claims 1, 39, 40 and new Claims 46 and 47 is found in the specification, for example, on page 25, lines 17-28; page 34, lines 3-7.

Support for the amendment to add the phrase "as compared to in the absence of administration of said compound" in amended Claim 1 and new Claims 45-47 is found in the specification, for example, on page 20, lines 1-3.

Support for new Claim 43 is found in the specification, for example, on page 58, lines 9-10; Example 3; and Figs 3A and 3B.

Support for new Claim 44 is found in the specification, for example, on page 26, lines 24-28.

Support for new Claim 45 (other than discussed above) is found in original Claim 1, and page 20, lines 1-3.

Support for new Claim 46 (other than discussed above) is found in the specification, for example, on page 13, line 19 to page 14, line 7.

Support for new Claim 47 is (other than discussed above) is found in the specification, for example, on page 25, line 23 to page 26, line 12; page 34, lines 3-7.

Declaration Under 37 CFR 1.131:

With regard to the previously submitted Declaration under 37 CFR 1.131, the Examiner has indicated that this submission was premature since no patent had issued from U.S. Patent Publication No. 2002/0037846A1 and no rejection had been made using that publication.

Applicants respectfully submit that it is believed that U.S. Patent Publication No. 2002/0037846A1 was available as prior art when it was submitted to the Examiner, because the application was refiled as a Continued Prosecution Application after November 29, 2000 and then published (i.e., it is the publication of the CPA that qualifies as prior art). On this basis, Applicants submitted the Declaration to attempt to expedite prosecution in the event that the Examiner determined that the publication should be cited under 35 U.S.C. § 102(e). In any event, U.S. Patent Publication No. 2002/0037846A1 has now issued as U.S. Patent No. 6,743,429, which is submitted herewith by Supplemental Information Disclosure Statement. If the Examiner now determines that U.S. Patent No. 6,743,429 should be cited, then Applicants respectfully request the full consideration of the Declaration submitted under 37 CFR 1.131. The Examiner has also indicated that submission of such a Declaration is inappropriate when the reference is claiming the same patentable invention, but Applicants are not aware that such a determination has yet been made by the Examiner.

Objection to the Specification and Rejection of Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. This rejection is maintained for the reasons of record. In response to Applicants' last response, the Examiner states that the specification only describes a method for inhibiting airway hyperresponsiveness (AHR) by administration of human αCGRP, and contends that the specification does not teach how to make any CGRP, nor which amino acids of full-length CGRP can be modified, or whether the resulting CGRP homologue retains the same function as CGRP. The Examiner again refers to Zhu et al. as

allegedly teaching that CGRP may play different physiological and pathophysiological roles in airway regulation in different species, and that Kanazawa et al. teach a fragment of CGRP (8-37) that is an antagonist.

Applicants traverse the Examiner's rejection under 35 U.S.C. § 112, first paragraph. Initially, Applicants note that in response to the Examiner's suggestion to amend the claims to more clearly recite that the CGRP fragments and homologues have a more specific biological activity that is reflective of CGRP agonist activity (to avoid any confusion that the claims could be referring to an antagonist peptide), the claims have been amended to recite that the homologues and fragments are CGRP agonists that "bind to and activate a CGRP receptor" or "have substantially the same or increased biological activity as compared to a naturally occurring CGRP peptide". Support for these amendments is discussed above. If the Examiner is still not satisfied with these amendments, Applicants would appreciate the Examiner's specific input as to what the Examiner feels is lacking from these descriptions.

Applicants again submit that a fragment or homologue of CGRP that has similar biological activity to the native peptide (e.g., an agonist) or that binds to and activates a CGRP receptor is reasonably expected to operate in a similar manner to the native CGRP peptide, such as the method of the present invention. For example, a homologue that binds to and activates a CGRP receptor in a similar manner as the native peptide is indicative of shared structural characteristics between the homologue and the native peptide that correlate with the function of the peptides. Given that the inventors have demonstrated that CGRP can inhibit allergen-induced AHR, it is submitted that any CGRP fragment, homologue, or even analog with substantially similar CGRP biological activity should be deemed suitable for use in the present invention.

Moreover, Applicants submit that the specification and the art provide sufficient guidance to one of skill in the art to readily make and use the recited homologues and peptides without undue experimentation. Specifically, during the interview, Applicants' agent reiterated the detailed discussion that was provided in the last response regarding the knowledge in the art and provided by the specification at the time of the invention regarding the structure and function of CGRP and fragments and homologues thereof. It was noted that all of this information appears in the Detailed Description of the invention, and includes incorporation by reference of several different publications

and database submissions, as well as the Examples. These publications provide the following cumulative information (details can be found in the prior response):

(1) isolation and full characterization of the α and β-forms of CGRP by amino acid sequencing and fast atom bombardment-mass spectrometry (FABMS);

(2) nucleic acid and amino acid sequence characterization of human CGRP, as well as methods of synthetically producing human CGRP;

(3) nucleic acid and amino acid sequences for CGRP from a variety of mammalian species (e.g., human, mouse, rat, dog, sheep);

(4) homology of CGRP among species is very high and the mouse and human CGRP peptides can be used interchangeably;

(5) amino acid positions 8-37 of CGRP has an antagonist function;

(6) agonist homologues of CGRP including substitutions at position 36; D-amino acid substitutions at minimally positions 36 and 37; and substitutions at position 35 are known in the art, as well as methods for determining the biological activity of CGRP.

In addition, in the response filed January 29, 2003, Applicants provided two additional references (U.S. Patent No. 4,720,483 and PCT Publication No. WO 89/03686), which describe a variety of functional derivatized CGRP homologues with biological activity similar to that of the native protein, including an alignment for comparison of structures. WO 89/03686 also provides direction as to where in the protein substitutions have different effects on the biological activity of the protein. U.S. Patent No. 5,122,376 (see Applicants' first 1449) also describes homologues of CGRP comprising substitutions and derivatizations.

Therefore, Applicants submit that it is completely unreasonable for the Examiner to assert that there is insufficient information available in the art and in the specification regarding the structure to function relationship of CGRP, or that the specification does not teach how to make or use the recited CGRP homologues and fragments, because the contrary is clearly true. Indeed, Applicants submit that the issues set forth in the Examiner's provisions of Stryer et al. and Ngo et al. are addressed by the knowledge already provided in the art. Given this abundance of guidance regarding the structure and function of CGRP and the description and knowledge in the art of many homologues that are functional agonists of CGRP, the enablement requirement is believed to be met.

The Examiner has not provided any specific argument that addresses how the multiple points of information, including examples in the art that meet the claim limitations above do not teach or suggest to one of skill in the art how to make a CGRP homologue or fragment having the claimed activity.

In the April 21 Office Action and during the interview, the Examiner again raised the issue of Zhu et al. as alleged evidence of the unpredictability of using any CGRP in the claimed method. Specifically, the Examiner states that Zhu et al. "teach that calcitonin gene-related peptide (CGRP) may play different physiological and pathophysiological roles in airway regulation in different species such as horse, human,[sic] Sprague-Dawley rat, and mouse". However, Applicants specifically addressed this position in the last filed response, but did not receive any particular reply to that argument from the Examiner. Again, Applicants submit that the conclusions of Zhu et al. do not merit the expansion of the findings to the conclusions proposed by the Examiner. Specifically, in contrast to the Examiner's characterization regarding Zhu et al., this publication states in the Discussion that "peptidergic nerves may play different physiological and pathophysiological roles in airway regulation in different species" (emphasis added). Clearly, the Examiner has inserted a reference to the substance CGRP in place of the actual reference to peptidergic nerves, which is not an appropriate substitution or in the proper context of Zhu et al. The study of Zhu et al. is directed primarily to the effect of *capsaicin* on sensory nerve fibers and they conclude that sensory neuropeptides such as SP or CGRP released from *capsaicin-sensitive* nerves have no *direct* effect on smooth muscle tone, although the possibility of indirect effects is not ruled out. This is a study of capsaicin sensitivity, and does not teach that CGRP from different species may have the effects concluded by the Examiner. If the Examiner intends to maintain this position with regard to Zhu et al., Applicants respectfully request that the Examiner address the differences cited by Applicants above.

With regard to Kanazawa et al., Applicants are aware that the 8-37 peptide is a CGRP antagonist, as this antagonist is used and discussed in the Examples of the present specification. The present claims do not encompass a CGRP antagonist. Moreover, Applicants submit that the knowledge that this fragment of CGRP is an antagonist only adds to the structure-to-function

knowledge in the art at the time of the invention, further enabling one of skill in the art to produce a CGRP agonist (i.e., obviously this peptide would be avoided).

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 under 35 U.S.C. § 112, first paragraph.

Objection to the Specification and Rejection of Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 under 35 U.S.C. § 112, first paragraph, on the basis of written description. The rejection is maintained for the reasons of record. In response to Applicants' last submission, the Examiner states that, other than human α CGRP, there is inadequate written description about the structure associated with all CGRP agents, and that terms without the amino acid sequence have no structure or function. The Examiner states that there is a lack of written description for any additional representative species.

Applicants traverse the rejection of Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 under 35 U.S.C. § 112, first paragraph. As discussed above, Applicants have amended the claims in the manner discussed with the Examiners during the October 6 interview. With regard to the issue of written description, the issue is whether, at the time the application was filed, the inventors have reasonably conveyed to those of skill in the art that they were in possession of the claimed invention. The Examiner has asserted that there is insufficient written description in the specification regarding the claimed homologues and fragments of CGRP, but Applicants refer to the prior response and also to the reiteration of this response in the enablement discussion above, and assert that the opposite is true. Again, the Detailed Description of the Invention (see pages 26, 27, 34, Examples) provides a description of the knowledge in the art at the time of filing regarding CGRP, the relationship of structure to function, and the description of several different homologues, fragments and analogs of CGRP, including ones that retained similar biological activity of the native peptide. As discussed previously, the specification does not merely allude to the structure of CGRP and fragments and homologues thereof, as the Examiner appears to assert, but provides specific definitions of such agents and several references to the known structure and function of the native CGRP peptides as

well as to various homologues thereof. Given that the inventors have demonstrated that CGRP can inhibit allergen-induced AHR, it is submitted that any CGRP fragment or homologue with substantially similar CGRP biological activity as the native peptide should be deemed suitable for use in the present invention, and Applicants submit that it is clear that the inventors were in possession of the claimed invention at the time of filing.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-10, 12-14, 20-30, 38-40 and 42 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38 and 42 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38 and 42 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Cadieux et al. Specifically, the Examiner contends that Cadieux et al. teach a method of inhibiting allergen-induced AHR in a mammal comprising administering a CGRP agent wherein the reference mammal has been sensitized to an allergen. The Examiner references Methods, Figure 2, page 237, column 2, page 241, column 2, third paragraph.

Applicants traverse the rejection of Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38 and 42 under 35 U.S.C. § 102(b). Applicants submit that Cadieux et al. fail to anticipate the invention because Cadieux et al. fail to teach or suggest each and every element of the claimed invention. Specifically, Applicants submit that Cadieux et al. fail to teach that the administration of CGRP to a mammal that has been sensitized to an allergen inhibits allergen-induced airway hyperresponsiveness in the mammal. Referring to Cadieux et al., page 239, col. 2, first paragraph of the Discussion, Cadieux et al. state that:

> "The results of this study demonstrate that in guinea pig airways, CGRP exerted a potent and dose-related inhibitory effect on SP-induced contraction both *in vitro* and *in vivo*." (emphasis added)

Further, at page 237, col. 1, second paragraph of the results, Cadieux et al. state that:

> "...SP injected intravenously elicited not only airway constriction by also transient systemic hypotension."

Finally, at page 236, col. 2, first full paragraph, Cadieux et al. state that:

"Only guinea pigs (control and OA-sensitized) showing a reasonable strong (>Hg) airway constriction to the cholinergic agonist were used in the study....SP which was used as the main spasmogen was injected intravenously every 20 min to induce brochoconstriction. Care was taken to choose a dose of SP so that the same extent of airway constriction could be induced in both animal groups." (emphasis added)

Therefore, the experimental model of Cadieux et al., whether performed in non-sensitized or OVA-sensitized guinea pigs, measures only the effect of CGRP on substance P (SP)-induced AHR. SP, which is a known sensory neuropeptide, potently induces bronchoconstriction in both non-sensitized and sensitized animals and therefore is not useful for distinguishing between other effects on the animals, such as allergen sensitization. Indeed, Cadieux et al. state that animals *were selected* to have the **same** response to SP, regardless of the OA-treatment, and thus, the experimental model of Cadieux et al. can not measure the effect of any agent on allergen-induced AHR, because the animals respond to SP regardless of the allergen-sensitization state of the animal. At best, the model of Cadieux et al. can measure the effect of inflammation on the CGRP effect on *SP-induced AHR*, which is does not teach the effect of CGRP on allergen-induced AHR. In fact, one can not tell at all from the experiments of Cadieux et al. whether or not the OA-sensitized guinea pigs were sufficiently sensitized to develop AHR in response to a proper provoking agent for measuring allergen-induced AHR, because this experiment was not performed (i.e., Cadieux et al. did not test for allergen-induced AHR), and because the animals were actually *selected* to *remove* any distinction from non-sensitized animals. The way the experiment is performed by Cadieux et al., since normal, non-sensitized animals have maximal AHR (same as allergen-sensitized) in the absence of any treatment, one can only measure the effect of an agent such as CGRP on the SP-induction of AHR.

Referring first to the *in vivo* study represented by Figure 2 of Cadieux et al., which is noted by the Examiner in the April 21 Office Action, one should initially take note that, in the absence of CGRP, both the control for the non-sensitized guinea pigs and for the OA-sensitized guinea pigs had similar and significant increases in airway resistance in response to SP. There is no control that shows what effect the OA-sensitization had on AHR, because SP induces bronchoconstriction *in all guinea pigs* and further, the guinea pigs having different treatments were selected, as stated by

Cadieux et al., to have the same response to SP. As shown in Figure 2, administration of CGRP to non-OA-sensitized animals inhibited SP-induced bronchoconstriction with statistical significance in a dose-dependent manner. In contrast, administration of CGRP to OA-sensitized animals resulted in no statistically significant inhibition of SP-induced AHR (see figure legend with regard to "Astericks"). From this result, one can conclude that allergen-sensitization appears to have *prevented* CGRP from inhibiting *SP-induced* AHR. This teaches nothing about the effects of CGRP on allergen-induced AHR and if anything, suggests that allergen-sensitization has an inhibitory effect on the action of CGRP in this model. If one even argues that there "appears" to be a modest reduction in the airway resistance at the highest dose of CGRP, as Cadieux et al. seem to portray the results (despite the lack of any statistical significance as admitted by Cadieux et al.), these results only show the effect of allergen-sensitization or local inflammation on an AHR process that would also occur in the ***absence*** of allergen-sensitization, and specifically show that the effect of allergen-sensitization was to *worsen* the ability of CGRP to inhibit this *SP-induced* AHR. In other words, at best, Figure 2 of Cadieux et al. shows that allergen-sensitization works against the ability of CGRP to inhibit *SP-induced AHR*, and teaches nothing about the effects of CGRP on allergen-induced AHR. Therefore, Cadieux et al. **fail** to teach a method of using CGRP to inhibit allergen-induced AHR.

Moreover, it is submitted that one of skill in the art can not infer from the teachings of Cadieux et al. that inhibition of allergen-induced AHR would have inherently been inhibited, because Cadieux et al. do not provide any demonstration that the animals had been sufficiently sensitized to test this possibility, because Cadieux et al. do not actually test this possibility at all in any of the experiments, because Cadieux et al. use SP-induction which causes bronchoconstriction whether or not the animals have been sensitized to allergen, and because Cadieux et al. actually introduce selection techniques that further disallow such inferences beyond what is actually demonstrated by *normalizing* bronchoconstriction in non-sensitized and OA-sensitized animals.

Similar results are seen in the experiment shown in Table 1 of Cadieux et al., which was reviewed in the October 6 interview, and which shows the effect of CGRP *in vitro* on SP-induced contractions of isolated bronchi and parenchymal strips that have been removed from OA-sensitized and non-sensitized guinea pigs. In this experiment, as discussed on page 236, col. 2, second and

third full paragraphs, the contraction produced in the presence of CGRP was compared to the mean of two control responses to SP observed prior to CGRP administration. Again, "the inhibitory effect of CGRP on contractions induced by SP was also examined at a dose of SP (5×10^{-8}) that induced similar maximal responses in tissues obtained from each group of animals", showing that as with the *in vivo* experiment, Cadieux et al. first *normalized* the responsiveness of both treatment groups to SP, further emphasizing and ensuring that the effect of the experiment was to measure *SP-induction of AHR*, and not AHR that is induced as a result of allergen-sensitization. Table 1 shows that in bronchi and strips from non-sensitized animals, CGRP was able to inhibit SP-induced contractions in a dose-dependent manner. In OA-sensitized animals, the effect of allergen-sensitization appeared to *inhibit the ability of CGRP* to inhibit SP-induced contractions, and in the main bronchi, CGRP failed to significantly prevent SP-induced contractions in OA-sensitized animals (see page 238, col 2, first paragraph). Again, at best, Table 1 shows the effect of allergen-sensitization on AHR that occurs in the *absence* of allergen-sensitization, and specifically shows that the effect of allergen-sensitization was to *worsen* the ability of CGRP to inhibit this *SP-induced* AHR. Table 1 of Cadieux et al. shows that allergen-sensitization works against the ability of CGRP to inhibit *SP-induced AHR*, and teaches nothing about the effects of CGRP on allergen-induced AHR.

Indeed, a careful review of the conclusions of Cadieux et al. shows (page 239, col.2, first paragraph of Discussion):

> "...the bronchoprotective effect offered by CGRP in both mammalian species was found to be strongly attenuated and even vanished in airway preparations showing clear manifestations of local inflammatory reaction." and on page 241, col. 2, last full paragraph:
>
> "...the braking effect of CGRP on SP-induced increase in airway resistance was markedly impaired in the OA-exposed guinea pigs when compared with control animals."

Therefore, Cadieux et al. do not measure the effects of CGRP on allergen-induced AHR and only reach the conclusion that the effects of allergen-sensitization or local inflammation was to *lessen* the ability of CGRP to inhibit AHR induced by the potent bronchoconstrictor, SP. This is simply not

a teaching of the claimed invention, which requires that allergen-induced AHR be inhibited by CGRP as compared to in the absence of CGRP.

In contrast, the method of the present invention is directed to the use of CGRP to inhibit allergen-induced AHR in mammals. The present inventors have demonstrated that CGRP inhibits allergen-induced AHR by using an art-accepted model of allergen-induced AHR, in which the allergen-sensitized animals, but not control animals, have a marked induction of AHR in response to the challenge stimulus. The control animals therefore serve as a baseline control, similar to normal human parameters for airway function (e.g., see page 14, line 26 to page 15, line 18). In this manner, one can directly measure AHR that is induced by allergen-sensitization of the animal (i.e., allergen-induced AHR), and thereby measure the ability of an administered agent (e.g., CGRP) to reduce allergen-induced AHR. As taught on page 18, lines 21-23 of the specification, and in contrast to any teaching of Cadieux et al.:

> "In the case of an allergen, the airway hyperresponsiveness is apparently or obviously, directly or indirectly triggered by an allergen to which a mammal has previously been sensitized."

Referring to Figs. 3A and 3B of the specification, for example, one can see that animals that are not sensitized to allergen (i.e., normal animals; SAL) have a baseline level of airway resistance and dynamic compliance as a result of exposure to the provoking agent. In contrast, animals that are sensitized to allergen and have not been treated (i.e., the AHR control demonstrating that allergen-induced AHR is what is being measured; OVA) have a marked increase in airway resistance and a marked decrease in dynamic compliance in a dose-dependent manner in response to challenge with the provoking agent. The administration of CGRP to the sensitized animals (CGRP) result in a substantially complete inhibition of AHR as one can clearly see by comparing to the SAL and OVA controls.

Therefore, it is submitted that in contrast to the present invention and what is presently claimed, Cadieux et al. do not teach or suggest a method for inhibiting allergen-induced AHR in a mammal that has or is at risk of developing allergen-induced AHR by administering CGRP or an agonist homologue or fragment thereof, wherein administration of the CGRP inhibits allergen-

induced airway hyperresponsiveness in the mammal as compared to in the absence of administration of said agent.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3-5, 8-9, 12, 20-21, 23, 25-26, 29, 38 and 42 under 35 U.S.C. § 102(b).

Rejection of Claims 1, 6-7, 10, 22, 24, 27, 30 and 40 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 6-7, 10, 22, 24, 27, 30 and 40 under 35 U.S.C. § 103, contending that these claims are unpatentable over Cadieux et al. in view of U.S. Patent No. 5,858,978 or U.S. Patent No. 5,635,478. Specifically, in addition to the alleged teachings of Cadieux discussed above, the Examiner contends that the '978 patent teaches a method of using CGRP for inhibiting acute or chronic inflammatory conditions such as asthma, which is associated with airway hyperresponsiveness due to constriction in human. The '478 patent is cited for allegedly teaching the same. The Examiner contends that it would have been obvious to substitute the CGRP of the Cadieux reference for the homologue of CGRP to inhibit allergen-induced AHR as allegedly taught by Cadieux, the '978 patent and the '478 patent. The Examiner asserts that the motivation to do so is provided by the '978 patent teaching that CGRP is useful for treating a variety of acute and chronic inflammatory respiratory disorders.

Applicants traverse the rejection under 35 U.S.C. § 103. Initially, Applicants refer to the discussion above with regard to Cadieux et al. and submit that, for these reasons, Cadieux et al. do not teach or suggest the presently claimed invention. Moreover, Applicants submit that the combination of Cadieux et al. with one or both of the '978 patent or the '478 patent do not remedy the deficiencies of Cadieux et al. alone. Indeed, even if one substitutes homologues of CGRP as stated by the Examiner, the combination does not teach or suggest the present invention. Moreover, as previously submitted, '978 patent and the '478 patent are directed to the use of CGRP to ameliorate inflammatory conditions by inhibiting the release of the proinflammatory cytokines, IL-1, or IL-1 and IL-2, from immune cells such as macrophages and lymphocytes. The use of CGRP is disclosed by these patents as being useful for the treatment of a wide variety of diseases, of which asthma is only one. Furthermore, Applicants traverse the Examiner's contention that either of the '978 or '478 patent teach or suggest anything about treating AHR (page 14, middle paragraph of the

April 21 Office Action); it is submitted that neither patent teaches or suggests treating AHR. Moreover, for the reasons of record, Applicants submit that asthma and AHR are not one in the same condition, but rather conditions that can be associated with one another, and neither of the '978 patent or the '478 patent teach or suggest treating AHR. Finally, as previously discussed, treatment of inflammation does not lead one of skill in the art to contemplate the treatment of AHR, because treatment of inflammation can occur in the absence of an effect on AHR, as these are separate conditions. Second, even with an association between inflammation and allergen-induced AHR, Applicants submit that the suggestion to inhibit the release of IL-1 or IL-1 and IL-2 in a patient with allergen-induced AHR or indeed, any allergic inflammation, including allergic asthma, is not consistent with, and in fact is *contrary to*, what is known about allergic inflammation by those of skill in the art, also previously discussed. This would represent a *teaching away* from the present invention.

Furthermore, given that Cadieux et al. do not teach or suggest that administration of CGRP can inhibit allergen-induced AHR and moreover, given that Cadieux et al. clearly teach that in an inflammatory condition such as allergen-sensitivity, the ability of CGRP to impact SP-induced bronchoconstriction is severely impaired, one would be *dissuaded*, and certainly not motivated to combine the references as the Examiner has done. Furthermore, the negative results of Cadieux et al. would not provide one of skill in the art with any expectation of success, even in combination with the teachings of the cited patents.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 6-7, 10, 22, 24, 27, 30 and 40 under 35 U.S.C. § 103.

Rejection of Claims 1, 25 and 27 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 25 and 27 under 35 U.S.C. § 103, contending that these claims are unpatentable over Cadieux et al. in view of Suissa et al. Specifically, in addition to the alleged teachings of Cadieux discussed above, the Examiner contends that Suissa et al. teach a combination of leukotriene receptor antagonist and beta agonist is more effective than beta agonist alone in treating mild to moderate asthma. The Examiner asserts that it would have therefore been obvious to combine the teachings of Suissa et al. with Cadieux et al. and that one of skill in the art

would have a reasonable expectation of success in producing the claimed invention, although no particular reason is provided for either statement Motivation is alleged based on the teachings of Suissa et al. regarding an improvement using the combination of leukotriene receptor antagonist and beta agonist.

Applicants traverse the rejection of Claims 1, 25 and 27 under 35 U.S.C. § 103. Again, Applicants refer to the discussion of Cadieux et al. above and submit that, for these reasons, Cadieux et al. do not teach or suggest the presently claimed invention. Moreover, Applicants submit that the combination of Cadieux et al. with Suissa et al. does not teach or suggest the present invention. Suissa et al. only teach that a combination of leukotriene receptor antagonist and beta agonist is more effective than beta agonist alone in treating mild to moderate asthma. Such a teaching does not provide any teaching whatsoever regarding CGRP, and so one must look to Cadieux et al. to provide the teaching, motivation and expectation of success within the combination. Clearly, there is no motivation provided by Cadieux et al., which *dissuades* one from using CGRP to treat AHR during inflammatory conditions, to perform a method using any other agents for asthma, nor can the combination correct the deficiencies of Cadieux et al. or provide any more expectation of success at making and using the presently claimed invention as compared to Cadieux et al. alone.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 25 and 27 under 35 U.S.C. § 103.

Rejection of Claims 1 and 27 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1 and 27 under 35 U.S.C. § 103, contending that these claims are unpatentable over Cadieux et al. in view of Drazen et al. or Abraham et al., or Abdelaziz et al., or Barnes et al. or Hoshino et al. Specifically, in addition to the alleged teachings of Cadieux discussed above, the Examiner cites the secondary references for various teachings of leukotriene receptor antagonists, cromolyn sodium, nedocromil, theophylline, and antihistamine. The Examiner asserts that it would have been obvious to combine the teachings of the references and that one of skill in the art would have a reasonable expectation of success in producing the claimed invention, although no particular reason is provided for either statement. Motivation is alleged based on the teachings of the secondary references to use the various compounds to treat AHR or inflammation.

Applicants traverse the rejection of Claims 1 and 27 under 35 U.S.C. § 103. Applicants refer to the discussion of Cadieux et al. above and submit that, for these reasons, Cadieux et al. do not teach or suggest the presently claimed invention. Moreover, Applicants submit that the combination of Cadieux et al. with any of the above-identified secondary references does not teach or suggest the present invention. These references only provide a teaching of various compounds that might be useful to treat asthma or inflammation. None of the references provides any teaching whatsoever regarding CGRP, and so one must look to Cadieux et al. to provide the teaching, motivation and expectation of success within the combination. Clearly, there is no motivation provided by Cadieux et al., which *dissuades* one from using CGRP to treat AHR during inflammatory conditions, to perform a method using any other agents for asthma, nor can the combination correct the deficiencies of Cadieux et al. or provide any more expectation of success at making and using the presently claimed invention as compared to Cadieux et al. alone.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1 and 27 under 35 U.S.C. § 103.

Rejection of Claims 1, 28 and 29 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1, 28 and 29 under 35 U.S.C. § 103, contending that these claims are unpatentable over Cadieux et al. in view of WO 98/03534. Specifically, in addition to the alleged teachings of Cadieux discussed above, the Examiner cites the WO publication as allegedly teaching various CGRP agonists such as CGRP-RCF analog that has the same biological activity as human CGRP. The Examiner contends that it would have been obvious to combine these teachings and that one of skill in the art would have a reasonable expectation of success in producing the claimed invention, although no particular reason is provided for either statement. Motivation is alleged because the WO publication allegedly teaches that the CGRP analog is useful for treating asthma.

Applicants traverse the rejection of Claims 1, 28, and 29 under 35 U.S.C. § 103. Applicants refer to the discussion of Cadieux et al. above and submit that, for these reasons, Cadieux et al. do not teach or suggest the presently claimed invention. As in the prior Office Actions in which the WO 98/03534 reference was used in a combination, the Examiner asserts that the CGRP-RCF of

WO 98/03534 is a CGRP agonist or antagonist. Applicants again disagree, and respectfully request that if the Examiner intends to maintain this rejection in the future, that the following comments be specifically addressed. It is Applicants' position that WO 98/03534 teach that CGRP-RCF is a *CGRP receptor component factor*, a 148 amino acid peptide which confers CGRP responsiveness to a CGRP receptor expressed by oocytes, apparently by allowing expression of the receptor. CGRP-RCF is not CGRP or an agonist or antagonist thereof. Page 16, lines 14-20 of WO 98/03534 teach that the receptor component factor refer to molecules *other than* CGRP receptor ligands or CGRP receptors. WO 98/03534 teach that CGRP-RCF might be useful to treat large number of virtually unrelated diseases. WO 98/03534 does not teach or suggest the use of CGRP or any compound to inhibit allergen-induced AHR and can not remedy the deficiencies of Cadieux et al. as discussed above, nor is there any motivation or expectation of success provided by the combination, because even with WO 98/03534, Cadieux et al. clearly *dissuades* one from using CGRP to treat AHR during inflammatory conditions.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 28, and 29 under 35 U.S.C. § 103.

Applicants have attempted to respond to all of the issues raised in the April 21 Office Action and submit that the claims are in a condition for allowance. In the event that the Examiner has any remaining concerns regarding the claims, the Examiner is encouraged to contact the below-named agent at (303) 863-9700 to expedite prosecution.

Respectfully submitted,

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